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An efficient synthesis of quinoxaline derivatives using HCTU as catalyst in DMF

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Abstract: We have successfully developed a novel and efficient method for the synthesis of quinoxaline and its derivatives. This method involves the reaction between various 1,2-diamines and substituted phenacyl bromides in the presence of a catalytic amount of *O*-(1H-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU) in dimethylformamide (DMF) as the solvent. This protocol offers several advantages, including mild reaction condition, short reaction time and moderate to high yield of the desired product(s).

Keywords: Quinoxalines; HCTU; 1,2-Diamines; phenacyl bromides.

1. Introduction

Quinoxalines are nitrogen-containing heterocyclic compounds. The functional derivatives of these heterocycles are recognized for their extensive biological applications such as antifungal,[1-2] anticancer,[3-4] antiviral,[5] kinase inhibitor,[6] biocidal[7] and anti-HIV activity against anti-HIV IIIB strains.[8] These heterocyclic compounds also find their importance in the other fields such as pharmaceuticals,[9] sensing of ions,[10-12] dye industries,[13] agro-chemicals,[14] organic semiconductors[15] and chemically controllable switches[16]. Looking to the applications of quinoxaline derivatives, enormous methodologies are developed for their synthesis. The most common method for the synthesis relies on the condensation of an aryl 1,2-diamines with 1,2-dicarbonyl compounds,[17-21]. Similarly, 1,2-keto hydroxyl compounds undergo reaction *via* tandem oxidation procedure involving catalysts such as $Pd(OAc)_2$,[22-23] MnO_2,[24] I_2/DMSO,[25-26]. Quinoxalines and its derivatives also synthesized by oxidative cyclization of α-haloketones and 1,2-diamines from epoxides,[27-28] and $CeCl_3.7H_2O$.[29] Several well-known catalysts and reagents were used in the synthesis of quinoxalines which include $RuCl_2(PPh_3)_3$,[30] $CuSO_4.5H_2O$,[31] PTSA,[32] TMSCl,[33] *N*-Bromosuccinimide,[34-36] T3PDMSO or T3P,[37] PEG-400,[38] ZnI_2,[39] $InCl_3$,[40] $Ga(OTf)_3$,[41] $ZrCl_4$,[42] $SbCl_3$,[43] $NbCl_5$,[44] and $ZnFe_2O_4$[45]. Similarly the synthetic methodology for quinoxalines using recyclable nano-catalysts have been reported in the literature[46]. Many of the established methods for synthesizing quinoxaline and its derivatives have faced certain limitations. These includes the use of costly transition metal-based catalysts, demanding reaction conditions, and

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the incorporation of hazardous or toxic organic solvents to achieve a satisfactory product yield. Hence, the need for advancing methods to synthesize quinoxaline derivatives has become a focal point in current research.

In synthetic organic chemistry, uronium salt-based coupling agents like TBTU, TATU, COMU and HBPyU have gained considerable attention. The catalysts mentioned above have been effectively employed in organic reactions, primarily functioning as dehydrating agents, for instance synthesis of glycopeptide,[47] for esterification[48] and for condensation reaction.[49] Our research group specializes in developing environmental friendly methods for synthesis of heterocyclic compounds. [50-53] We have discovered that uronium salts can serve as an efficient Lewis acid catalyst in heterocyclic compound synthesis.[54] Therefore, we intend to report the use of uronium salt i.e. *O*-(1*H*-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (figure 1) as a Lewis acid catalyst to achieve the targeted compounds. Recently, catalysts have become increasingly significant, primarily due to their positive impact on both the environment and the economy. They have proven effective in various organic transformations, minimizing the production of undesirable waste materials.

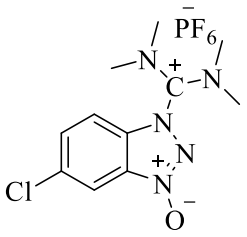


Figure 1. *O*-(1*H*-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

2. Experimental

2.1. General Methods

All the chemicals, catalyst and reagents were purchased from Merck. Solvents were distilled before use. The progress of reactions was monitored by thin layer chromatography with TLC Silica gel 60 F_{254} purchased from Merck. Column chromatography was performed on silica gel (60–120 mesh). Melting points were recorded by an open glass capillary sealed at one end melting point tube. The IR spectra were recorded on PerkinElmer Frontier FT-IR spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Ultra shield, Avance II model NMR spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR are reported in parts per million (ppm) from tetramethyl silane (TMS) as an internal standard in $CDCl_3$ /DMSO-d_6 as a solvent. Mass spectra were recorded on AB SCIEX QTRAP 3200 model LC-MS spectrophotometer.

2.2. General Procedure

In a 50 mL round-bottom flask, 1,2-diamine (1.0 mmol) and phenacyl bromide (1.0 mmol) were stirred at room temperature for 5 minutes. Then, HCTU (30 mol%) in 5 mL DMF was added to the reaction mixture. The progress of the reaction was monitored using TLC. After the reaction was completed, the product was extracted with ethyl acetate (EtOAc) three times (5 mL each), dried over anhydrous Na_2SO_4, filtered and evaporated the same under reduced pressure. The resulting material was further purified by silica gel column chromatography (60–120 mesh) using an EtOAc-petroleum ether (5:95) mixture to get the pure product.

2.3. Spectral Data for Compounds

2-Phenylquinoxaline (3a)[33]: yellow solid; mp 75-76[55] °C; IR (solid, KBr, ν_{max}, cm^{-1}) 2920, 2850, 2360, 1541, 1444, 1122, 1076, 954, 669, 549; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.26-8.04 (m, 4H), 7.77 (m, 2H), 7.63-7.45 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.86, 143.38, 142.32, 141.61, 136.80,

130.28, 130.19, 129.64, 129.54, 129.16, 127.56; LC-MS *m/z* $[M-1]^-$ 205.1; Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.45; H, 4.81; N, 13.49.

6-Nitro-2-phenylquinoxaline (3b) [62]: brown solid; mp 165 -168 °C Lit.[55]; IR (solid, KBr, ν_{max}, cm^{-1}) 2920, 2358, 1521, 1350, 1078, 964, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.03 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.31-8.24 (m, 3H), 7.62 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.34, 147.47, 145.51, 144.94, 140.37, 135.65, 131.42, 131.20, 129.44, 127.96, 125.69, 123.80; LC-MS *m/z* $[M-1]^-$ 249.0; Anal. Calcd for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.73; O, 12.74. Found: C, 66.85; H, 3.55; N, 16.65; O, 12.69.

6-Methoxy-2-phenylquinoxaline (3c) [62]*:* white crystalline solid; mp 73-76 °C Lit.[56]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.15 (s, 2H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.54 (m, 4H), 7.12 (m, 1H), 4.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 152.0, 144.1, 140.8, 137.9, 137.1, 130.1, 129.2, 127.6, 123.0, 107.0, 55.9.

6-Fluoro-2-phenylquinoxaline (3d) [63]*:* light yellow solid; mp 96-98 ºC, Lit. [57]; IR (solid, KBr, ν_{max}, cm^{-1}) 3026, 2922, 2852, 1618, 1541, 1161, 1024, 881, 835, 522; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.20-8.16 (m, 2H), 8.10 (d, *J* = 9.2, 1H), 7.76 (d, *J* = 9.3, 1H), 7.60-7.48 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (d), 152.49, 143.22 (d), 142.65, 138.82 (d), 136.41, 130.50, 129.21, 127.63, 119.97, 113.15, 112.98; LC-MS *m/z* $[M]^+$ 224.9; Anal. Calcd for $C_{14}H_9FN_2$: C, 74.99; H, 4.05; F, 8.47; N, 12.49. Found: C, 74.89; H, 3.99; F, 8.38; N, 12.40.

6-Chloro-2-phenylquinoxaline (3e) [62]**:** light brown crystalline solid; mp 146-147 ºC, Lit. [58]; IR (solid, KBr, ν_{max}, cm^{-1}) 3047, 2920, 2362, 1805, 1600, 1481, 1132, 1072, 958, 904, 588; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.21-8.16 (m, 2H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.67 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.61-7.50 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.52, 143.41, 142.63, 140.09, 136.08, 130.55, 129.21, 128.49, 127.60; LC-MS *m/z* $[M-1]^-$ 238.8; Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; Cl, 14.73; N, 11.64. Found: C, 69.81; H, 3.69; Cl, 14.68; N, 11.59.

2-(4-methylphenyl)quinoxaline (3f) [33]: white solid, mp 97 ºC, Lit.[59]; IR (solid, KBr, ν_{max}, cm^{-1}) 3676, 2970, 2920, 2360, 1615, 1577, 1489, 1124, 1045, 829, 555; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.12 (d, 8.0 Hz, 4H), 7.79-7.68 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.82, 143.31, 142.33, 141.46, 140.49, 133.99, 130.18, 129.89, 129.54, 129.27, 129.10, 127.42, 21.42; LC-MS *m/z* $[M+1]^+$ 221.3; Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.71; H, 5.39; N, 12.65.

6-fluoro-2-(4-methylphenyl)quinoxaline (3g) [64]: yellow solid, mp 135 °C, Lit.[60]; IR (solid, KBr, ν_{max}, cm^{-1}) 2920, 2850, 2360, 1606, 1543, 1425, 1184, 1159, 721; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.10 (m, 2H), 7.75 (d, *J* = 9.4, 1H), 7.61-7.42 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H); LC-MS *m/z* $[M-1]^-$ 237.3; Anal. Calcd for $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; F, 7.97; N, 11.76. Found: C, 75.58; H, 4.59; F, 7.91; N, 11.69.

2-(4-Chlorophenyl)quinoxaline (3h) [33]*:* yellow solid, mp 134-135 °C, Lit.[60]; IR (solid, KBr, ν_{max}, cm^{-1}) 2918, 2850, 2360, 1591, 1209, 1122, 1089, 715; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.14 (d, 7.8 Hz, 4H), 7.81-7.69 (m, 2H), 7.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.59, 142.88, 142.23, 141.68, 136.59, 135.20, 130.48, 129.79, 129.61, 129.41, 129.19, 128.78; LC-MS *m/z* $[M+1]^+$ 241.2; Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; Cl, 14.73; N, 11.64. Found: C, 69.78; H, 3.71; Cl, 14.65; N, 11.57.

6-fluoro-2-(4-chlorophenyl)quinoxaline (3i): light brown; mp 147-151°C; IR (solid, KBr, ν_{max}, cm^{-1}) 3086, 2970, 2357, 1591, 1433, 1249, 1012, 713, 516; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.30-7.90 (m, 3H), 7.76 (d, *J* = 9.2, 1H), 7.55 (m, 3H); LC-MS *m/z* $[M+1]^+$ 259.1; Anal. Calcd for $C_{14}H_8ClFN_2$: C, 65.00; H, 3.12; Cl, 13.70; F, 7.34; N, 10.83; N, 11.64. Found: C, 64.92; H, 3.05; Cl, 13.63; F, 7.29; N, 10.77.

6-methoxy-2-(4-chlorophenyl)quinoxaline (3j) [62]**:** yellow solid, mp 157-160 °C; IR (solid, KBr, ν_{max}, cm^{-1}) 2848, 2360, 1620, 1462, 1219, 1051, 719; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8 Hz, 1H), 7.50-7.51 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.74, 148.30, 143.20, 142.69, 138.33, 135.99, 135.39, 130.53, 129.30, 128.38, 123.80, 106.51, 55.84; LC-MS *m/z* $[M]^+$ 270.7; Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; Cl, 13.09; N, 10.35; O, 5.91. Found: C, 66.49; H, 4.08; Cl, 13.00; N, 10.28; O, 5.84.

7-Bromo-2-phenylpyrido[2,3-b]pyrazine (3k)[60]: mp 154.5-155.0 °C, Lit. [61]; IR (solid, KBr, ν_{max}, cm^{-1}) 3321, 2972,2883, 2358, 1541, 1377, 1087, 879, 669; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 4.2 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.37-7.33 (m, 3H), 7.13 (m, 2H); LC-MS *m/z* $[M-1]^-$ 285.5; Anal. Calcd for $C_{13}H_8BrN_3$: C, 54.57; H, 2.82; Br, 27.93; N, 14.69. Found: C, 54.51; H, 2.76; Br, 27.85; N, 14.61.

3. Results and Discussion

As a part of our efforts to develop efficient and environment friendly synthetic method, [38] we have explored the synthesis of quinoxaline and its derivatives. This is achieved by reacting different 1,2-diamines and substituted phenacyl bromides in the presence of HCTU, which serves as a cost-effective and eco-friendly Lewis acid catalyst for this organic transformations.

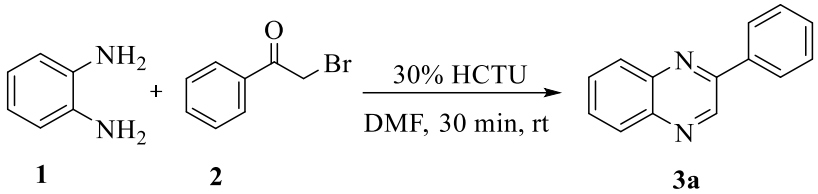
Initially, a model reaction was designed involving *O*-phenylenediamine (1) (1.0 mmol, 0.108 g) and Phenacyl bromide (2) (1.0 mmol, 0.199 g) in 5 mL of ethanol. After stirring at room temperature for five minutes, a catalytic amount of HCTU (*O*-(1H-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (30 mol%, 0.123 g) was added to the reaction mixture (Scheme 1). Subsequently, the reaction contents were stirred at room temperature. After 30 minutes, the completion of the reaction was verified using TLC. To optimize the reaction conditions, various solvents and different catalyst loadings were tested on the model reaction. Initially, the impact of various solvents on the reaction conditions was examined and it was observed that as the polarity of the solvent increased, the product yield also increased with a shorter reaction time (Table 1, entries 1, 3, 4 & 5). In the case of water, the product yield remained very low even after 100 minutes of stirring at room temperature, likely due to the limited solubility of the starting materials in water (Table 1, entry 6).

Table 1. Study of an effect of solvents and catalyst on the reaction condition

Entry[a]	Solvents	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	Ethanol	5	50	52
2	DCM	5	80	38
3	THF	5	48	56
4	DMSO	5	45	58
5	DMF	5	42	61
6	Water	5	100	30
7	DMF	10	39	65
8	DMF	15	35	68
9	DMF	20	35	72
10	DMF	25	33	80
11	**DMF**	**30**	**30**	**90**
12	DMF	35	30	91
13	DMF	40	28	91

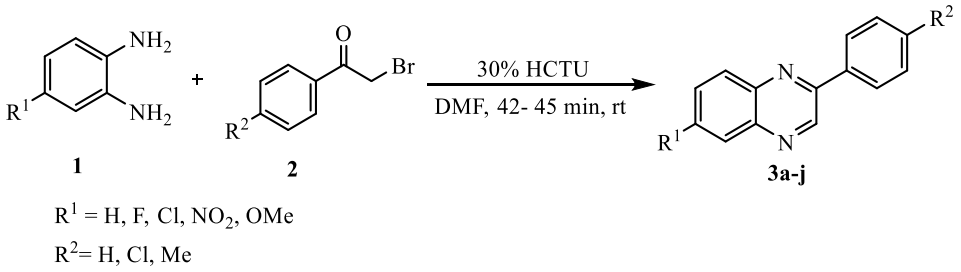
[a] The reaction was carried out at room temperature

[b] Isolated yield of the product.



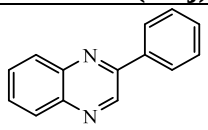
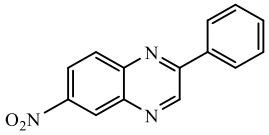
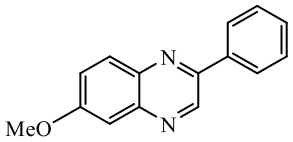
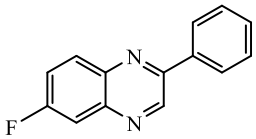
Scheme 1. Model reaction between *O*-phenylenediamine and Phenacyl bromide

After conducting solvent studies it has been observed that DMF was determined to be the most suitable solvent for this reaction (Table 1, entry 11). Similarly, the impact of different percentages of catalyst loading was assessed in the DMF solvent. It was found that as the percentage of the catalyst increased, the chemical yield of the reaction also increased, and the required reaction time decreased (Table 1, entries 7-11). Interestingly, no significant effect on reaction time and overall yield of the product was observed when the catalyst loading exceeded 35 mol% and 40 mol%, respectively (Table 1, entries 12 & 13). Therefore, the optimized reaction condition was established, resulting in a 90% yield of the product (Table 1, entry 11).

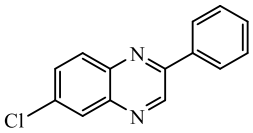
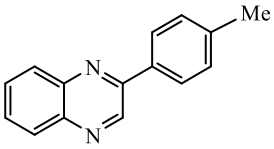
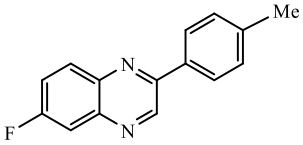
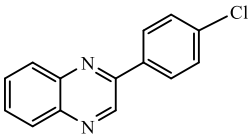
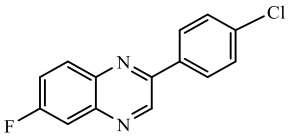
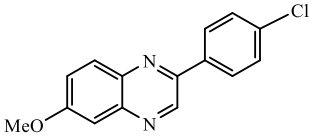


Scheme 2. Synthesis of various quinoxaline derivatives

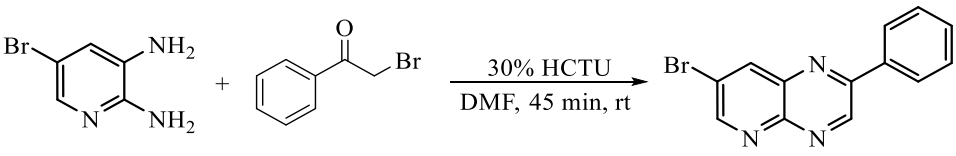
Table 2. Synthesis of quinoxaline derivatives using 1,2-diamines and phenacyl bromides under optimized reaction condition.

Entry[3a-j]	1,2-diamines (1)	Phenacyl bromide (2)	Product (3a-j)	Time (min)	Yield[b] %
3a	R^1= H	R^2= H		45	90
3b	R^1= NO_2	R^2= H		42	93
3c	R^1= OMe	R^2= H		45	83
3d	R^1= F	R^2= H		42	92

HCTU-catalyzed, DMF mediated synthesis of quinoxalines

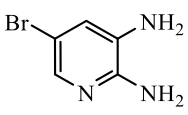
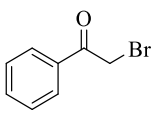
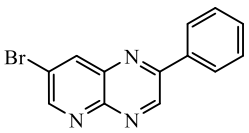
3e	R^1= Cl	R^2= H		45	91
3f	R^1= H	R^2= Me		45	90
3g	R^1= F	R^2= Me		42	94
3h	R^1= H	R^2= Cl		45	90
3i	R^1= F	R^2= Cl		42	94
3j	R^1= OMe	R^2= Cl		48	82

[a] Dissolving 1,2-diamines 1 (1.0 mmol) and various phenacyl bromides 2 (2.0 mmol) in 5 ml of DMF, we achieved the final product with a good yield after 42-45 minutes of continuous stirring. All the products (3a-j) were identified using IR, ^{1}H, and ^{13}C NMR.
[b] Isolated yield of the product.



Scheme 3. Synthesis of 7-bromo-2-phenylpyrido[2,3-b]pyrazine (**3k**)

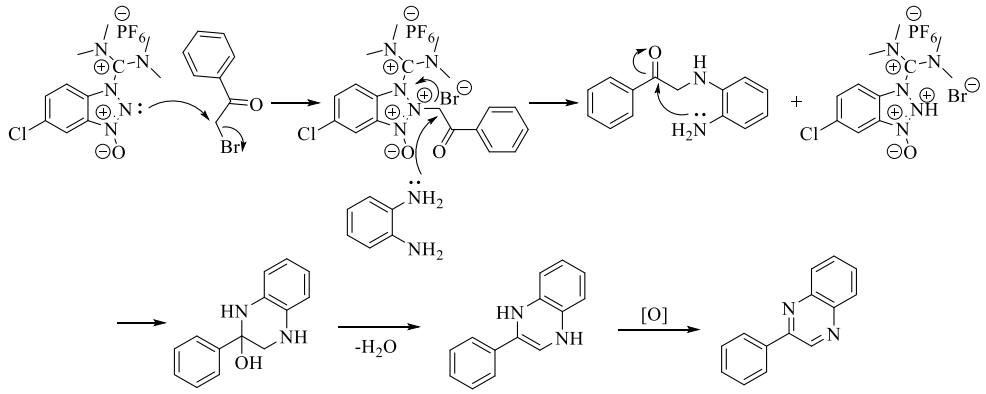
Table 3. Reaction of 5-bromo 2,3-diaminopyride and 3,3’ diaminobenzidine with phenacyl bromide

Entry[3k-l]	**1,2, dimine (1)**	**Phenacyl bromide (2)**	**Product (3k)**	**Time (min)**	**Yield[b] %**
3k				45	90

[a] By dissolving 5-Bromopyridine-2,3-diamine (1.0 mmol) and phenacyl bromide in 5 ml of DMF, the desired product was obtained after 45 minutes of continuous stirring. The product (3k) was identified through IR, ^{1}H, and ^{13}C NMR.
[b] Isolated yield of the product.

For generality of this protocol and to examine the substrate scope, various aromatic, heteroaromatic and substituted 1,2-diamines were reacted with substituted phenacyl bromides under the optimized reaction condition (Scheme 2 and 3). The result shows that *O*-phenylenediamine reacts efficiently with substituted phenacyl bromides to afford final product in moderate yield (Table 2, entry 3a, 3f & 3h). When, 1,2-diamine and phenacyl bromide holds electron withdrawing groups the reaction proceeds quickly with an excellent product yield (Table 2, entry 3i) with minimal reaction time. The presence of electron-withdrawing groups attached to the 1,2-diamine molecule seems to accelerate the reaction with phenacyl bromide, leading to a higher yield of the product. (Table 2, entry 3b, 3d, 3e, & 3g). Similarly, when 1,2-diamine possesses electron donating groups gave comparably lesser yield of the desired product (Table 2, entry 3c & 3j). However, 5-bromopyridine-2,3-diamine reacted smoothly with phenacyl bromide under the optimized reaction condition and gives 7-bromo-2-phenylpyrido[2,3-b]pyrazine in the moderate yield (Table 3, entry 3k).

The plausible reaction mechanism is illustrated in (Scheme 4). In Step 1, HCTU attacks the active methylene carbon of phenacyl bromide, forming an HCTU bromonium salt. In Step 2, one of the amine groups from *O*-phenylenediamine attacks the active methylene carbon, weakening the HCTU bond. In Step 3, another amine group from *O*-phenylenediamine attacks the carbonyl carbon, leading to the elimination of water and subsequent oxidation, resulting in the formation of quinoxaline as the product.



Scheme 4. Plausible reaction mechanism for the synthesis of quinoxaline

4. Conclusion

To conclude, we have successfully developed a method for synthesizing quinoxaline derivatives utilizing HCTU as a catalyst in DMF solvent under mild and straightforward reaction condition. This method yields the desired product with good to moderate efficiency when various 1,2-diamines and phenacyl bromides are employed. Notable advantages of this methodology include shorter reaction time, ease of catalyst handling and the ability to carry out reactions at room temperature.

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Supporting Information

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